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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/340,196	06/28/1999	RYOJI KATO	990701	3596

23850 7590 10/21/2002

ARMSTRONG,WESTERMAN & HATTORI, LLP
1725 K STREET, NW.
SUITE 1000
WASHINGTON, DC 20006

EXAMINER	
HOLLERAN, ANNE L	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 10/21/2002

24

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/340,196	Applicant(s) KATO ET AL.	
	Examiner Anne Holleran	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *51,53,54,56,59 and 68-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,53,54,56,59 and 68-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). *21* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Upon further consideration of the finality of the rejection of the last Office action, the finality of that action is withdrawn.

2. The amendment filed July 9, 2002 is acknowledged. Claims 49, 50, 52, 55, 57, 58 and 60-67 have been canceled. Claims 53, 59, 76 and 77 have been amended.

Claims 51, 53, 54, 56, 59 and 68-77 are pending and examined on the merits.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections Withdrawn:

4. The rejections of record of claims 49-77 under 35 U.S.C. 103(a) are withdrawn are withdrawn upon further consideration.

5. The rejections of record of claims 49-77 under 35 U.S.C. 112, 1rst paragraph are withdrawn upon further consideration.

Claim Rejections Maintained and New Grounds of Rejection:

6. Claims 51, 53, 54, 56, 59, 68, 69, 73, 74, and 77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamamoto (Yamamoto et al, Eur. J. Biochem. 143: 133-144, 1984) in

view of Benita (Benita et al, Eur. J Nucl. Med., 6: 515-52-, 1981) and further in view of Canfield (WO/87/00289).

The methods of claims 51, 53, 54, 56, 59, 68, 69, 73, 74, and 77 comprise determining a ratio of a first type of thyroglobulin to total thyroglobulin, or of a second type of thyroglobulin to total thyroglobulin, and relating this ratio to the determination of malignancy when the ratio is significantly higher or lower than that of a reference sample. The sample is a fluid sample originating from a living body. The first type of thyroglobulin is one that is reactive with a lectin or a first antibody. The second type of thyroglobulin is one that is not reactive with the lectin or first antibody that reacts with the first type of thyroglobulin.

Yamamoto teaches that thyroglobulin isolated from thyroid tumor tissue contains less sialic acid, contains less high-mannose type carbohydrate moieties, contains oligosaccharides of high molecular mass with repeating Gal-GlcNAc disaccharides and peripheral alpha-fucosyl residues than does thyroglobulin isolated from normal tumor tissue. Yamamoto also teaches that using the lectin ConA, one can differentiate between thyroglobulin isolated from malignant thyroid from thyroglobulin isolated from normal thyroid. ConA affinity chromatography demonstrates that thyroglobulin from malignant thyroids contains more triantenary complex-type oligosaccharides than thyroglobulin from normal thyroids; RCA affinity chromatography demonstrates that thyroglobulin from malignant thyroids has a greater amount of asialo complex-type carbohydrate chains than does thyroglobulin from normal thyroids. Thus, Yamamoto provides teachings that allow one or ordinary skill in the art to predict that lectin affinity may be used as the basis for an assay to differentiate between thyroblobulin secreted from a thyroid tumor from thyroglobulin secreted from a non-cancerous thyroid.

Yamamoto fails to teach a method comprising simultaneous use of lectins and anti-thyroglobulin antibodies for the determination of malignancy, and fails to teach measurements of thyroglobulin derived from fluid samples originating from a living body.

Benita teaches that thyroglobulin is a protein that is secreted into the blood, and teaches an immunoassay of serum thyroglobulin.

Canfield teaches the simultaneous use of lectins and antibodies for the measurement of thyroglobulin.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made methods comprising the use of lectins that differentially bound to the different sugar structures present of thyroglobulin derived from thyroid tumors, and the use of antibodies that bound to the non-carbohydrate portion of thyroglobulin and to use serum samples as the starting material, because the prior art teaches that thyroglobulin isolated from thyroid tumors contains different carbohydrate moieties than does thyroglobulin isolated from non-cancerous thyroids, where the difference in carbohydrates may be detectable through differential affinity to lectins. Because of the difference in lectin affinity, one of ordinary skill in the art would have had had a reasonable expectation of success in making a method that relied on the calculation and comparison of ratios of a first or second type of thyroglobulin to total thyroglobulin. For example, if amount of asialo complex-type thyroglobulin is a first type and sialo complex-type is a second type of thyroglobulin, then one of ordinary skill in the art would have had a reasonable expectation of success in observing a different ratio of first or second type of thyroglobulin to total thyroglobulin. One or ordinary skill in the art would have been motivated to use serum samples because of the ease and

convenience of serum samples as opposed to using biopsied thyroid samples. One of ordinary skill in the art would have seen the necessity of using a second antibody that bound to all types of thyroglobulin as taught by Canfield in order to increase the specifity of the assay, because lectins bind to carbohydrate moieties that might be present on other serum glycoproteins.

7. Claims 51, 53, 54, 56, 59, 68, 69, 73, 74, and 77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tarutani (Tarutani and Ui, J. Biochem., 98: 851-857, 1985) in view of Benita (Benita et al, Eur. J Nucl. Med., 6: 515-52-, 1981) and further in view of Canfield (WO/87/00289).

Tarutani teaches that thyroglobulin derived from thyroid tumors exhibits different Con A affinity than does thyroglobulin derived from normal tumors (page 853-854). Benita and Canfield teach as discussed above. Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made methods comprising the use of lectins that differentially bound to the different sugar structures present of thyroglobulin derived from thyroid tumors, and the use of antibodies that bound to the non-carbohydrate portion of thyroglobulin and to use serum samples as the starting material, because Tarutani teaches that there is a difference in lectin affinity between thyroglobulin derived from thyroid tumors from thyroglobulin derived from non-cancerous thyroids. Because of the difference in lectin affinity, one of ordinary skill in the art would have had had a reasonable expectation of success in making a method that relied on the calculation and comparison of ratios of a first or second type of thyroglobulin to total thyroglobulin. One or ordinary skill in the art would have been motivated to use serum samples because of the ease and convenience of serum samples as

opposed to using biopsied thyroid samples. One of ordinary skill in the art would have seen the necessity of using a second antibody that bound to all types of thyroglobulin as taught by Canfield in order to increase the specifity of the assay, because lectins bind to carbohydrate moieties that might be present on other serum glycoproteins.

8. Claims 70-72, 75 and 77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tarutani (Tarutani and Ui, J. Biochem., 98: 851-857, 1985) or Yamamoto (Yamamoto et al, Eur. J. Biochem. 143: 133-144, 1984) in view of Benita (Benita et al, Eur. J Nucl. Med., 6: 515-52-, 1981) and Canfield (WO/87/00289) and further in view of Robbins (U.S. 5,902,725; issued May 11, 1999; effective filing July 3, 1996).

The methods of claims 70-72, 75 and 77 comprise determining a ratio of a first type of thyroglobulin to total thyroglobulin, or of a second type of thyroglobulin to total thyroglobulin, and relating this ratio to the determination of malignancy when the ratio is significantly higher or lower than that of a reference sample, and comprises employing an antibody that binds to both types of thyroglobulin, but does not bind to thyroglobulin that is already bound to a lectin or antibody that binds to a sugar chain of the first type of thyroglobulin.

The teachings of Tarutani, Yamamoto, Benita and Canfield are set forth above. Each of these references fails to teach an assay that would employ an antibody that does not bind to an antigen already bound by a lectin or another antibody. Such an assays appears to be known in the art as an inhibition assay. Robbins teaches the combined use of lectins and antibodies to detect different oligosaccharide moieties of prostate specific antigen and specifically teaches the use of an inhibition assay in which an antibody that does not bind to PSA already bound to a

lectin is used (col. 6, line 57 – col. 7, line 18). Thus, because Tarutani or Yamamoto teach that thyroglobulin from thyroid tumors is differentially glycosylated, and because the concept of the inhibition assay is known in the art, it would have been prima facie obvious to one of ordinary skill in the art to have made an assay that comprised the use of an antibody that does not bind to thyroglobulin that is already bound to a lectin or an antibody that binds to the sugar chain of the first type of thyroglobulin.

9. Claims 51, 53, 54, 56, 59 and 68-77 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods based on differential lectin binding, does not reasonably provide enablement for methods based on differential binding of antibodies specfic for Lewis type sugar chains. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation would be required to practice the full scope of the claimed inventions are: 1) quantity of experimentation necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See Ex parte Forman, 230 USPQ 546, BPAI, 1986.

Because of the presence of claim 76, which is drawn to methods comprising the use of an antibody that is specific for a Lewis type sugar chain, claims 51, 53, 54, 56, 59 and 68-77 may be interpreted as drawn to methods where the first specific antibody is an antibody that binds to a

Lewis type sugar chain, where the Lewis type sugar chain is present in one type of thyroglobulin, but not in a second type of thyroglobulin.

The specification appears to contemplate the use of antibodies or lectins that specifically bind to Lewis type sugar chains, but provides no evidence that two types of thyroglobulin exist where one type has a Lewis type sugar chain and a second type lacks a Lewis type sugar chain, and that this differential glycosylation of thyroglobulin is associated with thyroid malignancy. Thus, further research to establish the relationship between the presence of Lewis type sugar chains on species of thyroglobulin and thyroid cancer would be required. Such research constitutes undue experimentation, because one of skill in the art would not have a reasonable expectation of success in establishing such a relationship. The working examples presented in the specification are not directed to methods comprising the determination of differential Lewis type sugar antigens on thyroglobulin, and the specification provides no guidance concerning the presence of Lewis type sugar antigens on thyroglobulin and any correlation with thyroid cancer. The specification provides no examples or guidance with respect to any antibodies that specifically bind to any of the Lewis type sugar chains and differential binding of these antibodies to different forms of thyroglobulin. Thus, the specification merely presents an invitation to experiment and does not provide the necessary support for the inventions as claimed.

10. Claim 75 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 75 is indefinite because of the and/or language, which allows methods that do not comprise performing steps (b)(ii) or (b)(iii). This is confusing because, for example, if the method comprises the step of (b)(iii) and not (b)(ii), the step of (b)(iii) requires information from step (b)(iii) and, therefore, cannot be performed.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

Anne L. Holleran
Patent Examiner
October 15, 2002

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600